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Letter to the Editor

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Mitochondrial Encephalopathy with CADASIL-Like MRI

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Dear Sir,

Mitochondrial cytopathies due to mitochondrial DNA (mtDNA) mutations represent a heterogeneous group of respiratory chain disorders associated with variable systemic, muscular, peripheral and central nervous system involvement. Heteroplasmy and a threshold effect are responsible for the variability of clinical manifestations. Prototypic neurological phenotypes include mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), myoclonus epilepsy with ragged-red fibers (MERRF), neuropathy, ataxia, and retinitis pigmentosa (NARP), and maternally inherited infantile subacute encephalomyelopathy (Leigh's syndrome) [1].

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant disorder caused by mutations in the *Notch3* gene. Clinically, CADASIL is characterized by recurrent ischemic strokes, migraine with or without aura, psychiatric symptoms, and cognitive decline, and it is assumed to be an underdiagnosed reason of ischemic stroke [2, 3]. Diagnosis of CADASIL is achieved by molecular genetic testing of the *Notch3* gene, or by skin biopsy revealing characteristic granular osmiophilic deposits in vascular smooth muscle cells [2, 4, 5]. Brain magnetic resonance imaging (MRI) reveals confluent hyperintense signals in the deep and periventricular white matter, characteristically in the temporal poles and the capsula extrema [6].

Herein we describe a patient with molecular genetically diagnosed mitochondrial cytopathy with MRI findings strongly resembling CADASIL.

Case Report

A 48-year-old woman was admitted to our department for the evaluation of bilateral ptosis and restricted eye movements. Her personal medical history was uneventful, and there were no neurological disorders reported from other family members. At the age of 45 years she noticed drooping eyelids, impaired visual ability at night, exercise-dependent leg weakness and fatigability. Over the following years, symptoms deteriorated and she had to give up her job as a sewer. In addition, she reported pulsating headaches without accompanying vegetative symptoms. She had no complaints regarding her memory, and she did not report epileptic seizures or stroke-like episodes.

General examination revealed short stature (1.48 m) and obesity. Neurological examination showed bilateral right-dominant ptosis and external ophthalmoplegia. Funduscopy as well as other cranial nerve functions were normal. There was no atrophy, muscle tone was normal, but there was moderate proximal paresis of the legs (M4 to M5; MRC grading). There was a slight bilateral brady-dysdiadochokinesia, and walking with closed eyes was slightly ataxic. Tendon reflexes were bilaterally weak, and plantar responses were flexor.

Laboratory workup showed elevated creatine kinase (190 U/I; normal for our laboratory <167) and serum lactate levels (3.4 mmol/l; normal <2.4), while serum glucose and pyruvate were within the normal range. EEG demonstrated slight general slowing with theta activity. Electroneurography and cardiologic investigations including echocardiography were normal. Biopsy of the left quadriceps revealed mild myopathic changes consisting of variability of fiber diameter, elongated fibers, and some internalized nuclei. Immunohistochemistry revealed no red ragged fibers (trichrome stain), and normal staining for mitochondrial enzyme activity (COX, NADH, and SDH stains). Electron microscopy of multiple skin and muscle vessels did not demonstrate granular osmiophilic deposits in the vascular smooth muscle cells.

Neuroradiology

MRI and magnetic resonance spectroscopy (MRS) were performed on a 3T Philips Achieva whole-body MRI system (Phil-

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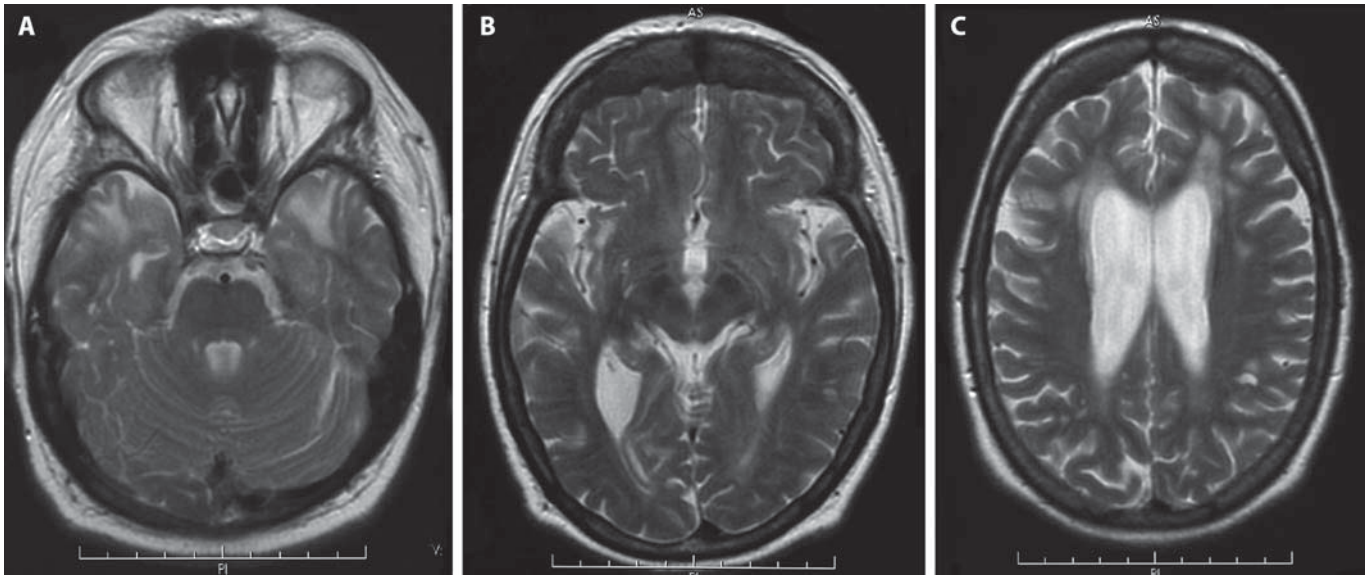

Fig. 1. MRI. **A**, **B** T_2-weighted MR images demonstrate confluent hyperintense signal alterations in the subcortical white matter of the anterior temporal poles (**A**) and the capsula extrema (**B**) bilaterally. **C** In addition, there are circumscribed hyperintense signal alterations in the subcortical cerebral white matter which are confluent in the frontal regions.

ips Medical Systems, Best, The Netherlands) using a transmit/receive head coil. T_2-weighted MRI sequences showed pronounced confluent hyperintense lesions in the white matter of the anterior temporal poles and marked hyperintense lesions in the capsula extrema bilaterally. In addition, there were some circumscribed hyperintense lesions in the subcortical white matter as well as confluent subcortical lesions in the frontal regions (fig. 1A–C). No lesions suspicious for microhemorrhages were detected and there was no pathological contrast enhancement. Diffusion-weighted imaging and ADC mapping have not been performed.

^{1}H-MRS data were acquired using high-resolution multi-spin echo spectroscopic imaging (TSI; TE = 288 ms, slice thickness = 1.5 cm, resolution 28 × 28, FOV = 220 mm) [7] and conventional chemical shift imaging (CSI; TE = 35 ms, resolution 16 × 16 and TE = 288 ms, resolution 12 × 12, NSA = 2; slice thickness = 2 cm, FOV = 220 mm). For all measurements the bandwidth was 2,500 Hz and the repetition time TR = 1,520. The data were received from axial slice, which was adjusted parallel to the calcarine fissure including the visual cortex. Regions of interest were selected in the subcortical white matter. Signal localization was achieved by use of point-resolved spectroscopy, and chemical shift selective excitation in combination with a dephasing gradient was used for water suppression. Spectral data were postprocessed using a constant baseline correction, B_0 correction, exponential spectral filtering by 2 Hz and Gaussian filtering of 3 Hz as well as linear phase correction. Relative metabolite concentrations were determined using LC Model. CSI showed a lactate double peak in the occipital cortical and subcortical brain regions bilaterally (fig. 2A). TSI revealed an alanine double peak in the frontal cortical brain regions (fig. 2B).

Molecular Genetic Analysis

Total DNA was extracted from EDTA-blood and skeletal muscle according to standard isolation protocols (Qiagen, Hilden, Germany). Screening for large-scale mtDNA rearrangements and point mutations was performed by long template polymerase chain reaction and single-strand conformation polymorphism, respectively. Abnormal conformers were directly sequenced on an ABI 377 DNA Sequencer (Applied Biosystems, Forster City, Calif., USA). No pathogenic point mutations but an 8.3-kb deletion in 28–36% of the mtDNA population of the muscle was detected. No deleted mtDNA was found in the blood. Amplification and sequencing of the entire *Notch3* gene on both strands and including exon-intron boundaries were performed using standard methods (Dr. R. Spiegel, Genetica, Human Genetic Laboratory, Zurich, Switzerland). No mutations were detected.

Discussion

A mitochondrial cytopathy in our patient was strongly suggested by the clinical pattern including short stature, progressive external ophthalmoplegia, and myopathy, as well as by the laboratory findings of elevated serum lactate and creatine kinase levels. The diagnosis was finally confirmed by molecular genetic analysis of the mitochondrial genome revealing a heteroplasmic 8.3-kb deletion in the skeletal muscle.

The CSI MRS results were in line with the diagnosis of a mitochondrial cytopathy and demonstrated a lactate doublet peak in occipital areas, reflecting a dysbalance between glycolysis and oxidative respiration. In addition, TSI MRS revealed a high alanine peak in the frontal lobe. Elevated alanine levels may be seen in patients with mitochondrial encephalopathy [8].

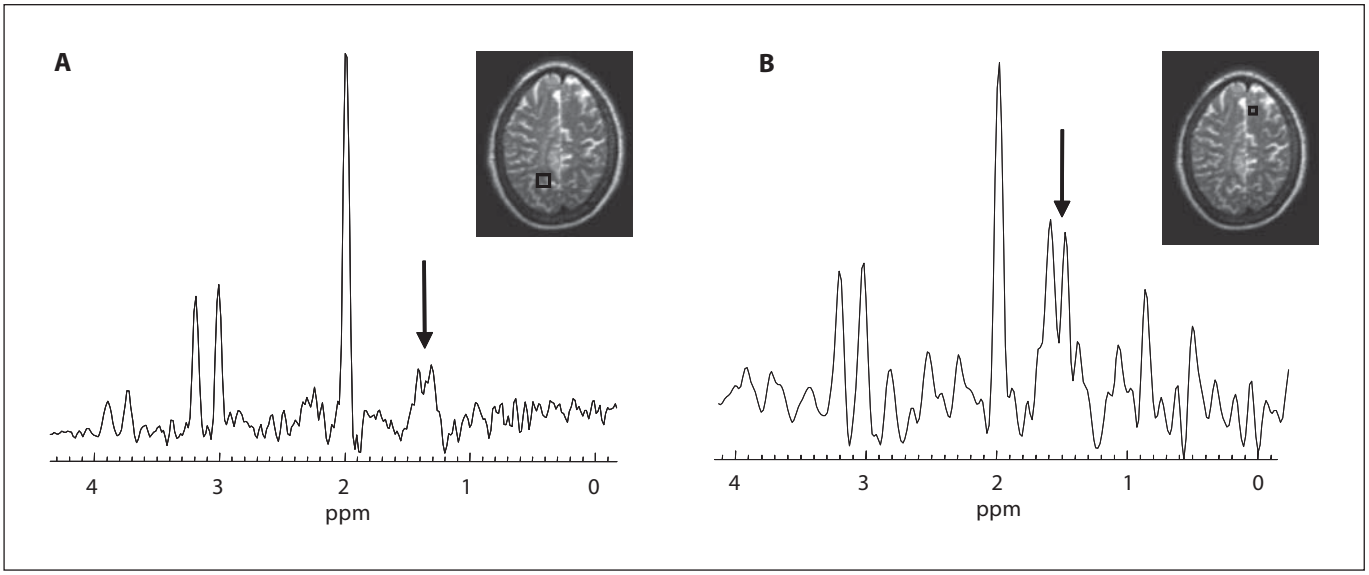

Fig. 2. MRS. **A** ^{1}H-MR spectrum, corresponding to the voxel shown in the right occipital region, obtained by CSI measurement, TE = 288 ms. The arrow indicates the lactate double peak at 1.33 ppm. **B** ^{1}H-MR spectrum, corresponding to the voxel shown in the left frontal region, obtained by TSI measurement, TE = 288 ms. The arrow indicates the alanine double peak at 1.48 ppm.

However, elevated alanine has also been described in animal models of ischemic brain injury, where it was interpreted as a general marker of ischemia [9, 10]. In contrast, main cerebral MRS findings in CADASIL patients included decreased N-acetyl aspartate, creatine and choline in pathological as well as normal-appearing white matter, whereas lactate was hardly visible in individual patient spectra and no alanine was detected [11].

Cerebral MRI alterations in mitochondrial encephalopathies are usually expected to be homogeneous and equally distributed in cortical and subcortical areas [12]. In our patient, however, there were circumscribed alterations in the anterior temporal poles, the capsula extrema and the subcortical white matter. This particular lesion pattern has been proposed to be suggestive of CADASIL [6, 13]. Compared to MRI alterations of patients with presumably sporadic cerebral small vessel disease without *Notch3* mutations, involvement of the temporal pole had a sensitivity of 89% and a specificity of 86% for the diagnosis of CADASIL [6]. Involvement of the external capsule was less specific and had a sensitivity of 93% and a low specificity of 45% [6].

Based on the negative skin biopsy and *Notch3* gene analysis, coincidental CADASIL in our patient can be practically excluded. Our findings therefore demonstrate an overlapping neuroradiological presentation of the two disorders. CADASIL and some phenotypes of mitochondrial encephalopathies also share several clinical characteristics such as migraine and stroke-like episodes, raising the question of common pathogenic mechanisms. Clinical peripheral nerve or muscle involvement, a hallmark of mitochondrial cytopathies, is not evident in CADASIL. However, several independent CADASIL families carrying different *Notch3* mutations had muscle mitochondrial abnormalities [14–16]. In a morphological study, abnormal mitochondria containing paracrystalline inclusions were detected, but these abnormalities were not associated with mitochondrial dysfunction or mtDNA mutations [16]. Another CADASIL patient had coincident mtDNA and *Notch3* mutations [14], and a recent study demonstrated an increased rate of mtDNA sequence variations within CADASIL pedigrees [17]. In addition, experimental data of a lethal mutation of the Drosophila Notch3 gene revealed a significantly decreased activity of two respiratory chain complexes, NADH dehydrogenase and ATP synthase [15].

In conclusion, mitochondrial encephalopathy may be associated with anterior temporal lobe changes thought to be specific of CADASIL. MRI and MRS studies might be useful tools in identifying overlap and co-occurrence of these two disorders, and might contribute to a better understanding of their pathophysiological intersections.

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References

1 DiMauro S, Schon EA: Mitochondrial respiratory-chain diseases. N Engl J Med 2003; 348:2656–2668.
2 Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cecillion M, Marechal E, Maciazek J, Vayssiere C, Cruaud C, Cabanis EA, Ruchoux MM, Weissenbach J, Bach JF, Bousser MG, Tournier-Lasserve E: Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. Nature 1996;383:707–710.

3 Jung HH, Bassetti C, Tournier-Lasserve E, Vahedi K, Arnaboldi M, Arifi VB, Burgunder JM: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: a clinicopathological and genetic study of a Swiss family. J Neurol Neurosurg Psychiatry 1995;59:138–143.
4 Ruchoux MM, Chabriat H, Bousser MG, Baudrimont M, Tournier-Lasserve E: Presence of ultrastructural arterial lesions in muscle and skin vessels of patients with CADASIL. Stroke 1994;25:2291–2292.
5 Jung HH, Rösler KM, Burgunder JM, Bassetti C: Peripheral nerve and muscle vessel lesions in CADASIL. Schweiz Arch Neurol Psychiatr 1996;147:148–150.
6 Markus HS, Martin RJ, Simpson MA, Dong YB, Ali N, Crosby AH, Powell JF: Diagnostic strategies in CADASIL. Neurology 2002;59:1134–1138.
7 Duyn JH, Moonen CT: Fast proton spectroscopic imaging of human brain using multiple spin-echoes. Magn Reson Med 1993;30:409–414.
8 Morava E, van den HL, Hol F, de Vries MC, Hogeveen M, Rodenburg RJ, Smeitink JA: Mitochondrial disease criteria: diagnostic applications in children. Neurology 2006;67:1823–1826.
9 Peeling J, Wong D, Sutherland GR: Nuclear magnetic resonance study of regional metabolism after forebrain ischemia in rats. Stroke 1989;20:633–640.
10 Griffin JL, Rae C, Dixon RM, Radda GK, Matthews PM: Excitatory amino acid synthesis in hypoxic brain slices: does alanine act as a substrate for glutamate production in hypoxia? J Neurochem 1998;71:2477–2486.
11 Auer DP, Schirmer T, Heidenreich JO, Herzog J, Putz B, Dichgans M: Altered white and gray matter metabolism in CADASIL: a proton MR spectroscopy and 1H-MRSI study. Neurology 2001;56:635–642.
12 Barragan-Campos HM, Vallee JN, Lo D, Barrera-Ramirez CF, Argote-Greene M, Sanchez-Guerrero J, Estanol B, Guillevin R, Chiras J: Brain magnetic resonance imaging findings in patients with mitochondrial cytopathies. Arch Neurol 2005;62:737–742.
13 Auer DP, Putz B, Gossl C, Elbel G, Gasser T, Dichgans M: Differential lesion patterns in CADASIL and sporadic subcortical arteriosclerotic encephalopathy: MR imaging study with statistical parametric group comparison. Radiology 2001;218:443–451.
14 Finnila S, Tuisku S, Herva R, Majamaa K: A novel mitochondrial DNA mutation and a mutation in the Notch3 gene in a patient with myopathy and CADASIL. J Mol Med 2001;79:641–647.
15 De La Pena P, Bornstein B, del Hoyo P, Fernandez-Moreno MA, Martin MA, Campos Y, Gomez-Escalonilla C, Molina JA, Cabello A, Arenas J, Garesse R: Mitochondrial dysfunction associated with a mutation in the Notch3 gene in a CADASIL family. Neurology 2001;57:1235–1238.
16 Malandrini A, Albani F, Palmeri S, Fattapposta F, Gambelli S, Berti G, Bracco A, Tammaro A, Calzavara S, Villanova M, Ferrari M, Rossi A, Carrera P: Asymptomatic cores and paracrystalline mitochondrial inclusions in CADASIL. Neurology 2002;59:617–620.
17 Annunen-Rasila J, Finnila S, Mykkanen K, Moilanen JS, Veijola J, Poyhonen M, Viitanen M, Kalimo H, Majamaa K: Mitochondrial DNA sequence variation and mutation rate in patients with CADASIL. Neurogenetics 2006;7:185–194.